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Effect of coronary artery diseases on ocular perfusion

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ABSTRACT

Objectives: This study aimed to evaluate the ocular perfusion of patients with ischemic coronary artery disease (CAD) using optical coherence tomography angiography.

Patients and methods: A total of 62 patients (49 male, 13 female; mean age: 62.9±9.1 years; range, 35 to 78 years) with a diagnosis of CAD were enrolled in this study. The data were compared with 61 healthy controls (35 male, 26 female; mean age: 68.1±3.9 years; range, 46 to 76 years). Coronary artery disease diagnosis was defined as patients who underwent percutaneous coronary intervention after coronary angiography. Optical coherence tomography angiography was used to assess the choroid thickness, superficial capillary plexus, and deep capillary plexus vascular density parameters of each patient.

Results: Choroid thickness was lower in the CAD group compared to the control group, but this decrease was not statistically significant. The results showed a significant decrease in superficial capillary plexus and deep capillary plexus parameters in CAD patients compared to healthy controls.

Conclusion: Patients with CAD showed decreased flow density compared to healthy controls. The study concludes that CAD patients exhibit reduced ocular perfusion, which can be detected using optical coherence tomography angiography. This noninvasive technique could be an effective tool for monitoring ocular perfusion and detecting vascular abnormalities in patients with CAD.

Keywords: Coronary artery disease, microvascular changes, ocular perfusion, optical coherence tomography angiography.

Coronary artery disease (CAD) is the most important cause of mortality and morbidity worldwide. Diagnosis requires a sequential approach, and the most currently accessible techniques to directly explore coronary vasculature are invasive. Precipitating factors of CAD include atherosclerosis, vasospasm, and a progressive chronic inflammatory process of arterial wall thickening or stenosis.[1] Several studies have shown a potential correlation between the coronary artery and many peripheral vessels in the human body, such as the cerebral, renal, and ocular vasculature.[2-4] Therefore, recent studies have suggested that ocular perfusion could serve as a promising marker for systemic vascular health.

The human retina, consisting of 10 layers, is supplied by two vascular beds: the retinal vessels and the choriocapillaris. The retinal vessels supply the inner layers of the retina that facilitate visual function, while the choriocapillaris provides oxygen and nutrients to the outer layers. The retinal vasculature, with blood vessels of a similar size to the coronary microvasculature, can be used as a representative of the subclinical coronary stenosis process. Due to the distinctive structure of the eyeball, fundus vasculopathy can be precisely detected by several examination techniques, including ophthalmoscopy, funduscopy, fundus photography, and fundus fluorescein angiography. Although fundus fluorescein angiography remains the gold standard in analyzing vascular and capillary

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beds despite its injection-related inconvenience and fluorescein side effects, optical coherence tomography angiography (OCTA), a novel noninvasive imaging modality that has gained importance in recent years due to its capability of imaging the microvasculature of retinal and choroidal vessels for diagnosing ophthalmological and systemic diseases. The evaluation and quantification of vascular density and blood flow across various anatomical layers of the fundus can be accomplished using OCTA.[5] This noninvasive imaging technique has proven useful as an early diagnostic tool for numerous ocular angiopathies, including age-related macular degeneration,[6,7] diabetic retinopathy,[8] and hypertensive retinopathy.[9] In addition, it also has the potential to provide insights into the microvascular changes that occur in different systemic diseases, including CAD.[10] The retinal microvasculature has been proposed as a proxy for coronary circulation in various publications, although there is still contrasting evidence on the strength of this relationship. This study aimed to investigate vascular changes in the retina and choroid of participants diagnosed with CAD through coronary angiography using OCTA.

PATIENTS AND METHODS

This prospective, cross-sectional, observational case-control study involving 62 patients (49 male, 13 female; mean age: 62.9±9.1 years; range, 35 to 78 years) with CAD and 61 age- and sex-matched healthy controls (35 male, 26 female; mean age: 68.1±3.9 years; range, 46 to 76 years). The CAD diagnosis was defined as patients who underwent percutaneous coronary intervention after coronary angiography by the same expert specialist. Patients diagnosed with acute coronary syndrome were not included in the study. Approximately half of the patients underwent right coronary artery intervention (n=29, 46,8%). Circumflex artery intervention was performed in 18 (29%) patients, and left anterior descending artery intervention was performed in 15 (24.2%) patients. Twenty-five (40.3%) patients underwent elective percutaneous intervention on the other untreated coronary artery. After an ophthalmic examination for ocular diseases, OCTA was performed on all patients. Optical coherence tomography angiography was performed using a commercially available OCTA device (AngioVue; Optovue Inc., Fremont, CA, USA). The superficial capillary plexus (SCP) and deep capillary plexus (DCP) vascular density parameters were measured and analyzed using the built-in AngioRetina software. Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the İzmir University of Economics Clinical Research Ethics Committee (date 11.01.2023, no: 2023/1). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria included the following: *(i)* definite diagnosis of CAD for the CAD group; *(ii)* being between 18 and 70 years of age; *(iii)* not having any previous disease that may affect the blood supply to the eye; *(iv)* not having any diseases that would prevent eye measurement. Coronary artery disease patients with moderate and high myopia/hyperopia (≥3 diopters or axial length ≥26 mm), any kind of glaucoma, dioptric media opacity that may affect OCTA imaging, and a history of any intraocular surgery or other fundus diseases were excluded. Patients with firm evidence of macular edema were also excluded. The control subjects had a best corrected visual acuity of 16/20 or better and underwent an ophthalmic examination to exclude glaucoma, cataract, fundus diseases, or other systemic diseases.

Optical coherence tomography angiography was performed to capture retinal and choroidal images using an AngioVue OCTA instrument (wavelength: 840 nm) and Avanti System version 2016.1.0. Optovue AngioVue software version 2016.1.0 (Optovue Inc., Fremont, CA, USA) was used to perform measurements of vessel density. The OCTA imaging software automatically fitted the examined zones based on the actual picture by the same examiner. In addition, the software automatically adjusted the specified margins while concurrently measuring the density of vessels. For OCTA, 100,000 A-scans are acquired per second to obtain images of the macula with a 3×3 mm^2. Five divided areas with the macula at the center are displayed, and the blood vessel density of each area is indicated as a percententage. The diameter of the inner circle is 1 mm, and the diameter of the outside circle is displayed at 3 mm (Figures 1, 2). The avascular zone of the fovea (mm^2) was then analyzed in the SCP and DCP OCTA of the macula. All patients were imaged in the same stage and under the same

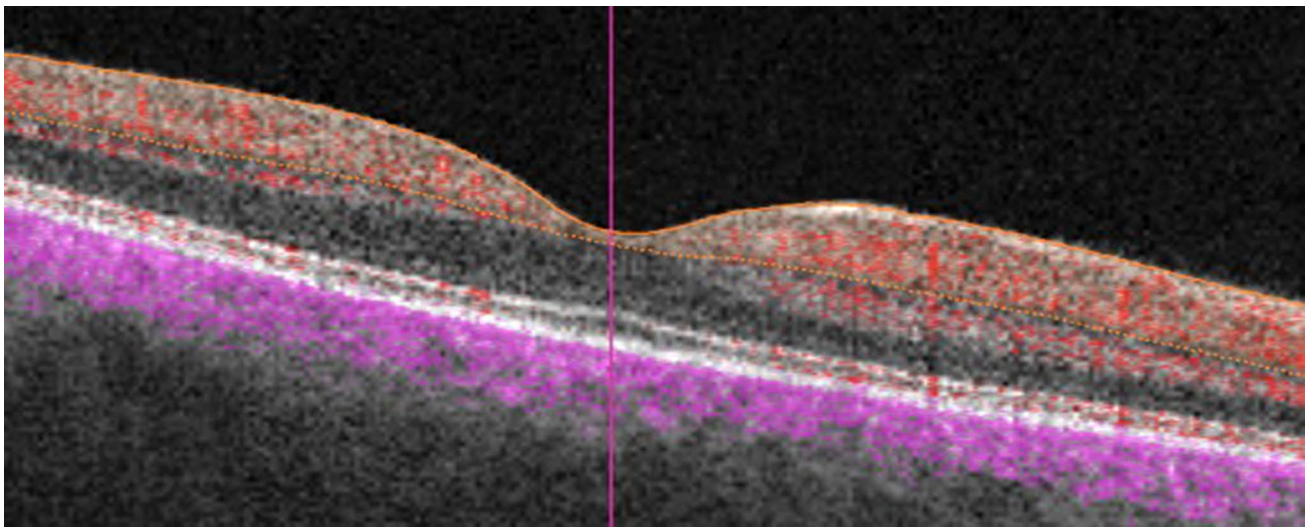

Figure 1. Cross-sectional image showing structural optical coherence tomography in the background and superficial vascular plexus data as a yellow overlay.

situations. Data reassessment was conducted by two independent, blinded examiners, followed by a final decision by a third blinded investigator in cases where discrepancies or disagreements arose during the assessments.

Statistical analysis

The statistical analysis of the study was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables that were examined, including vessel density, were presented as means ± standard deviation (SD). The differences between the two groups were evaluated through the chi-square test and two sample t-test. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

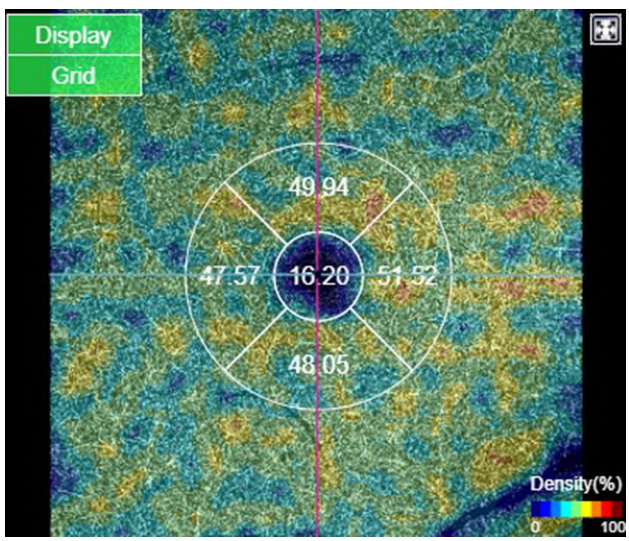

Figure 2. Vascular density in five regions, including the fovea (1-mm diameter), temporal, inferior, nasal, and superior quadrants (1-mm annular ring).

RESULTS

There were no significant differences in age, sex, or intraocular pressure between the two groups (Table 1). Patients diagnosed with CAD and volunteers participating in the control group did not have systemic diseases, such as hypertension, diabetes mellitus, heart failure, moderate/severe heart valve disease, thyroid dysfunction, or liver and kidney failure. No statistically significant difference was detected in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels in blood samples between the groups. No statistically significant differences were detected between the patient group and the control group in terms of echocardiographic parameters. Choroid thickness was lower in the CAD group compared to the control group, but this decrease was not statistically significant (286.42±78.93 μm *vs.* 309.32±72.93 μm). Superficial capillary plexus was significantly lower in the CAD group compared to the control group (15.4±2.1% *vs.* 16.9±3.4%; p=0.003). Deep capillary

Table 1
Demographic features and intraocular pressure of the study and control groups

	CAD group (n=62)			Control group (n=61)		
	n	%	Mean±SD	n	%	Mean±SD
Age (year)			62.9±9.1			68.1±3.9
Sex						
Female	13	20.9		26	42.6	
Male	49	79.1		35	57.4	
Intraocular pressure (mmHg)			16.05±3.13			14.55±3.50

CAD: Coronary artery disease; SD: Standard deviation.

plexus was also considerably lower in the CAD group compared to the control group (14.4±2.4% *vs.* 16.8±5.0%; p=0.001; Table 2).

DISCUSSION

Previous studies have provided limited data supporting the association between retinal microvasculature changes and CAD. In one such study, Tabatabaee et al.[3] demonstrated a strong correlation between retinal arterial atherosclerosis and the extent and severity of CAD using fundus photography. In addition, Wong et al.[11] confirmed the link between retinal arteriolar narrowing and the development of CAD by measuring the diameters of individual arterioles and venules on retinal photographs.

Arnould et al.[10] carried out a study where they compared the superficial retinal layer (SRL) vascular length (VL) of 44 healthy individuals to that of 237 patients who had been hospitalized for acute coronary syndrome. They found that in the parafoveal zone (excluding the central fovea), there was a significant decrease in SRL VL after matching 44 healthy individuals with 44 hospitalized patients.[10,12] The study established a connection between the retinal microvascular features and the cardiovascular risk profile of hospitalized patients. Patients with a lower VL were generally older and had a higher incidence of high blood pressure and diabetes mellitus. They also had a lower left ventricular ejection fraction and worse biological parameters, such as higher blood glucose, glycated hemoglobin A1c (HbA1c), creatinine, and N-terminal probrain natriuretic peptide. The study also identified two independent parameters, namely left ventricular ejection fraction and the burden of cardiovascular risk factors assessed by the American Heart Association risk score, which were negatively associated with the VL. Additionally, Arnould et al.[10] found moderate correlations between VL and two risk scores: Global Registry of Acute Coronary Events and the Reduction of Atherothrombosis for Continued Health. They also investigated the relationship between OCTA measured VL and hemodynamic variables in patients with myocardial infarction both during the acute phase and three months after cardiac rehabilitation.[13,14]

Table 2
Choroid thickness, SCP, and DCP perfusion in the study and control groups

	CAD group	Control group
	Mean±SD	Mean±SD
OCTA choroid (μm)	286.42±78.93	309.32±72.93
OCTA SCP (%)	15.4±2.1*	16.9±3.4*
OCTA DCP (%)	14.4±2.4*	16.8±5.0*

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CAD: Coronary artery disease; SD: Standard deviation; OCTA: Optical coherence tomography angiography; * p<0.05.

The study did not reveal any notable distinctions between the two time points or the OCTA parameters and cardiac hemodynamic variables, whether they were acute or chronic, such as left ventricular ejection fraction, aortic blood flow, systolic blood pressure, diastolic blood pressure, and cardiac output. This implies that the regulation of retinal microvasculature is not influenced by that of systemic circulation, indicating that it is self-regulated. However, it is important to note that the study did not assess the VL in the deep retinal layer (DRL), and the number of participants in the study was limited.[13]

Wang et al.[15] conducted a study that used OCTA to examine the relationship between vessel density, blood flow in the retina and choroid, and CAD. Their findings indicated a significant reduction in vessel density and flow area in most zones, except for SRL and DRL in the fovea in CAD patients. The researchers further analyzed the correlation between the changes in fundus microvasculature and the Gensini score, which reflects the severity of stenosis, in each coronary artery branch. They discovered that the degree of stenosis in the left main coronary artery, proximal left circumflex artery, and right coronary artery had a significant negative association with VD changes in the SRL and DRL. Proximal stenosis of the left anterior descending artery had a negative relationship with VD in the DRL. In terms of choroidal flow changes, negative correlations were found between this parameter and the severity of stenosis in the left main coronary artery, proximal left circumflex artery, and right coronary artery.[15]

In summary, the research outcomes indicate that OCTA has the potential to offer valuable insights into microvascular alterations linked to cardiovascular diseases and the capability to identify diminished ocular perfusion among patients with CAD. According to this investigation, there was a significant decline in the SCP and DCP vessel density metrics in CAD patients compared to their healthy counterparts. These findings indicate that patients with CAD experience a reduction in ocular perfusion, which may be associated with systemic vascular dysfunction.[10] Additionally, several investigations have highlighted the correlation between OCTA parameters and the severity or progression of CAD, suggesting that OCTA could serve as a noninvasive biomarker with clinical utility for predicting the risk of cardiovascular disease.[14]

The use of OCTA as a means of monitoring ocular perfusion and identifying vascular irregularities in patients with CAD could be a viable option. Nevertheless, additional investigations are required to validate these results and explore the possible contributions of OCTA in managing CAD patients. The conclusions of our research indicate that OCTA could be employed as a screening method for the prompt detection of CAD in populations with a high risk of the condition.

Furthermore, we found that OCTA is a reliable and noninvasive method for detecting early-stage CAD in high-risk patients showing reduced retinal vessel density, choroidal vessel density, and flow area. Therefore, early interventions such as percutaneous coronary intervention should be actively pursued to prevent myocardial infarction in such patients. Regular ophthalmic follow-up for high-risk patients may also effectively reduce the morbidity of ocular complications.

Previous studies have assessed the relationship between retinal vascular changes and CAD. For instance, a study including 109 CAD patients demonstrated a strong correlation between the degree of retinal arterial atherosclerosis and the severity and extent of CAD.[16] Some studies have also suggested that the diameter of retinal vessels, particularly arterioles, may predict the risk of CAD and stroke-related deaths in middle-aged individuals, which suggests that microvascular changes may contribute to the development of CAD.[15,17]

Our study revealed a decrease in both the SCP and DCP among patients with CAD. These results indicate that minor modifications in retinal vascularization could potentially function as early warning signals of cardiovascular disease, allowing cardiologists to intervene promptly. As a result, implementing this approach may prove successful in minimizing the frequency of myocardial infarctions.

Several theories have been suggested to account for these findings. Atherosclerotic alterations in the fundus vessels have been linked to thickening of the microvascular wall, lipid buildup, fibrosis, and calcification of larger arteries. Consequently, retinal arteriolar narrowing triggers premature microvascular injury. Individuals with CAD exhibit similar pathological characteristics in their coronary arteries as those found in the fundus vessels. As a result, changes in retinal or choroidal microvasculature may mirror systemic macrovascular modifications, particularly in instances of coronary artery stenosis.[15,16]

Although coronary angiography is the recognized benchmark for diagnosing cardiovascular diseases, it has some disadvantages, including adverse reactions and injuries caused by the contrast agent. Consequently, in some cases, there is a preference for less invasive techniques. One such approach is coronary computed tomography angiography, which offers several benefits over traditional angiography. Nevertheless, it is unsuitable for some vulnerable patients. In these instances, OCTA

provides a novel, noninvasive, drug-free diagnostic alternative.[15,18,19]

Several limitations were present in our study, including a homogeneous population, a relatively limited sample size, and a lack of long-term follow-up. Additionally, our study exhibited low statistical power due to its relatively limited sample size.

In conclusion, this study revealed a reduction in vessel density across various retinal layers in CAD patients, despite the absence of any observable clinical symptoms. These outcomes imply that CAD individuals may experience retinal vascular harm at an early stage. Optical coherence tomography angiography proves to be an effective and precise diagnostic method for detecting early-stage retina and choroid damage in CAD patients. Further comprehensive and longitudinal investigations are essential to substantiate these findings.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the research, acquisition of data, analysis and interpretation of the data, Statistical analysis and Obtaining financing, writing of the manuscript: C.T., S.G., T.O., O.U.F.; Critical revision of the manuscript for content: C.T., T.O., O.U.F.

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